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ABSTRACT

The three articles in this issue of a periodical focussed on various aspects of the life and health of children in the tropics concern: (1) immune defenses; (2) interactions between nutrition disorders and infection; and (3) immunity and vaccination. The science of immunology has progressed rapidly in recent years. A brief review of present scientific understanding of immune defenses is presented. It is noted that most public health-oriented research on individual nutritional status points to the existence of interactions between infection and nutrition disorders. Practical aspects of this interaction are discussed. Also addressed is the issue of when, and against which diseases, women, mothers, and children in physiologically difficult situations should be immunized. (RH)

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CHILDREN IN THE TROPICS

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IMMUNITY AND NUTRITION

1990 - N° 189

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INTERNATIONAL CHILDREN'S CENTRE – PARIS

The International Children's Centre was created by the French government in 1949, on the initiative of Professor Robert Debré in particular, following negociations between France and the United Nations. Its purpose was to furnish those international and national agencies dealing specifically with child care with training facilities and educational and information tools in the field of child health and development, viewing children within their family and surroundings.

ICC soon turned essentially toward Th. World children and devoted its activities to the training and education of personnel with social, educational and administrative responsabilities as well as medical and paramedical workers. The desire for greater efficiency has led it to work increasingly with trainers and to concentrate its efforts on the methodological and educational aspects of mother and child care programmes.

ICC is also engaged in an attempt to further study — and — action on some aspects of the life and health of children and their family, so as to contribute to practical improvement, particularly in the fields of growth, nutrition, planned parenthood, the control of transmissible and nutritional diseases, preschool and school education, the needs of disabled and underprivileged children, etc.

Over this period of more than 30 years, a large amount of documents on children and adolescents, mostly from the developing countries, has been accumulated. This international documentation has been classified and sorted out, and has been computerized since 1983 : a bibliographic data base (BIRD : « Base d'Informations Robert Debré ») may be consulted anywhere in the world, through international communications networks. ICC also publishes periodicals, educational documents and specialized bibliographic bulletins.

As for its legal status, the International Children's Centre is a foundation under french law of recognized public utility, administered by an executive board with broad international membership.

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CHILDREN
IN THE TROPICS
REVIEW OF THE INTERNATIONAL CHILDREN'S CENTRE

IMMUNITY AND NUTRITION

☐ HENRI DUPIN
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1990 - N° 189

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IMMUNE DEFENSES

by Henri DUPIN

CHARACTERISTICS OF THE IMMUNE RESPONSE

Through its immune reactions the body is capable :

— of recognizing foreign substances : bacteria, viruses and other micro-organisms, non-microbial allergenic substances, or foreign cells (grafts and transplanted organs, or cells that have become abnormal) ;

— of reacting against what is recognized as a foreign element, and of neutralizing or destroying it ;

Three features characterize the immune response :

— it is aimed against whatever is recognized as foreign to the body,

— it is specific,

— it is memorized ; this means that certain cells retain the memory of the antigenic structure, and make sure that the response is more rapid and more intense in case of a second aggression by the same agent.

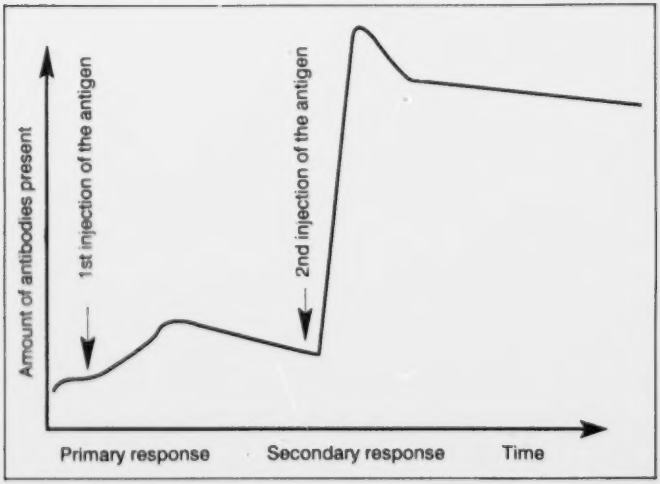

Figure 1 : The immune response is "memorized". In case of a second contact with the antigen, the response is much more rapid and more intense than the first reaction to the same antigen.

Every complex animal, including mammals and of course all human beings, is capable of recogizing what is "self" and "non-self" ; that is, of distinguishing all of the components of its own body from anything foreign. This is quite a remarkable property, since the human organism contains approximately 60,000 different proteins, each of which is recognized as "self", whereas a foreign protein is recognized as "non-self", or foreign. Some of these 60,000 different types of protein are present in large quantities within each of the thousands of billions of cells in our body, whereas others are less abundant or are only produced by a certain specific cells.

Neonates, whose body is composed of several hundred billion cells, also possess about 60,000 different proteins. During embryonic and foetal life, the immune system learns to distinguish between "self" and "non-self". However, immune defences are still incomplete at birth and during the first months of life.

In fact, the immune system does tolerate some very close relatives ; that is, some molecules whose characteristics closely resemble those contained in our own body.

This small margin of tolerance makes three types of action possible :

— blood transfusions : compatibility is checked for the A, B, O blood groups and for the Rh system, but there are actually over 80 blood groups systems, and it is impossible, in practice, to test for total compatibility ;

— organ transplants : the best possible compatibility is sought, using the system of tissue groups discovered by Professor DAUSSET, but there are no two individuals anywhere in the world (with the exception of monozygous twins) who possess exactly the same tissue groups ;

— the therapeutic use of certain substances — and particularly of hormones — taken from animals : for instance, the insulin administered to patients with diabetes mellitus is extracted from the pancreas of pigs or beef cattle. The protein chain of a molecule of swine or beef insulin differs only very slightly (by only one or two amino acids) from human insulin. This slight difference is generally tolerated by the human body.

SPECIFIC AND NON-SPECIFIC REACTIONS

The immune system is composed of two different but somewhat complementary types of action :

Non-specific immunity

Non-specific immunity constitutes the first line of defence in stopping the progression of pathogenic micro-organisms before infection actually develops.

It involves :

— the skin and mucous membranes, which are natural barriers,

— secretions, such as the lysozymes present in certain secretions,

— the "normal" bacterial flora present in the intestine, which prevents the multiplication of other bacterial species. However, this action may be insufficient ; in this case, the pathogenic microbial species proliferates in the digestive tract and disorders such as diarrhoea, alimentary toxinfections, etc. occur,

— cells, including polymorphonuclear neutrophils and especially macrophages, with a phagocytic action - that is, capable of capturing and digesting particles or micro-organisms. Phagocytosis by cells capable of this action is substantially increased by the presence of molecules produced by specific immune responses.

Specific immunity

Specific immunity is much more precise and complex than the non-specific system described above.

It involves the intervention of B lymphocytes, agents of humoral immunity - that is, of the production of specific antibodies against any one or several antigens aggressing the organism. It also makes use of the T lymphocytes, of which there are several groups that are directly responsible for cell-mediated immunity.

THE LYMPHOID ORGANS

The stem cells are located in the bone marrow. The spleen, a large-sized filter and reservoir organ attached to the blood circulation, is the seat of numerous interconnections involved in immunity.

The lymph nodes and tonsils are also lymphoid organs. Lymphoid tissue is present in the intestinal mucosa (Peyer's patches).

The thymus is a lymphoid organ located in the upper, anterior portion of the thorax. Its development begins early in the foetal evolution and continues throughout childhood ; the volume of the thymus declines gradually from puberty on. As will be seen further on, the thymus plays an essential role in the evolution of T lymphocytes, their maturation and the acquisition of immunocompetence.

CELL POPULATIONS AND IMMUNE RESPONSE

The following cell populations play a role in immune responses :

— polymorphonuclear neutrophils, which participate in phagocytosis and evacuate cell fragments. Their action is of the "non-specific" type ;

— the macrophages, which are also a product of the stem cells in the bone marrow : these are relatively large cells, the cytoplasm of which contains many lysosomes rich in enzymes active in lysis. They are capable of moving rapidly to the site of microbial invasion, and possess the ability to phagocyte micro-organisms and other foreign substances, as well as aged cells.

Phagocytosis

Phagocytosis includes three phases :

— adherence of the particle (or micro-organism) to the membrane of the macrophage,

— inclusion of this particle within the cytoplasmic vacuole,

— digestion of the particle by enzymes.

The breakdown of the antigen by macrophages is incomplete. These partially deteriorated antigens are "presented" to the lymphocytes, so that the latter will be able to recognize them subsequently : this is an important phase in the immune reaction.

Further, the macrophages then secrete soluble proteins : gamma interferon, and above all interleukin 1, which stimulate those T lymphocytes that have "recognized" the antigen.

Lymphocytes

The lymphocytes are produced by the stem cells in the bone marrow, and represent approximately 20 % of all leukocytes (whereas the other 80 % are polymorphonuclears). The outer membrane (or cytoplasmic membrane) of the lymphocytes contains many surface receptors that are capable of specifically binding a well-defined molecule.

The remarkable specificity of the immune reaction results from the fact that the surface receptor is able to react with a given antigen, to the exclusion of all others. Once they have developed sensitivity to an antigen, some lymphocytes are transformed into lymphoblasts, after which they proliferate.

There are two groups of lymphocytes : B lymphocytes and T lymphocytes. Those lymphocytes that reach maturity in the thymus through the action of the thymic hormones are known as Thymodependent, and are designated by the letter T. Conversely, when the lymphocytes reach maturity in the bone marrow — in mammals — and in a saclike lymphoid organ in birds, they are designated by the letter B.

Careful differentiation of these two groups (or populations) is important, since the mechanisms by which the T and B lymphocytes act and their role in the body's defensive reactions are quite different. The T lymphocytes are responsible for "cell-mediated immunity" ; there are several sub-groups of T lymphocytes (as will be seen farther down), and they do not play the same role.

B lymphocytes and the plasmocytes that are derived from them, produce the specific antibody corresponding to the antigen causing the immune reaction. Antibody = immunoglobulin. This is humoral immunity.

In addition, some lymphocytes are neither T nor B. These include the Killer or Natural Killer lymphocytes, in particular.

The two groups of lymphocytes — T and B — play complementary roles, in fact : they work in close cooperation. More specifically, the T lymphocytes stimulate, control and interrupt the production of antibodies by the B lymphocytes and the plasmocytes, as needed.

When the immune system is subjected to an antigen, it reacts by multiplying the cells sensitized by this antigen : the T and B lymphocytes, as well as killer lymphocytes. But there are some lymphocytes whose function is to retain the memory of the antigenic structure : these are the "memory cells", or primed cells. As a result, the body is prepared to respond extremely rapidly and effectively when it is again faced with the same antigen.

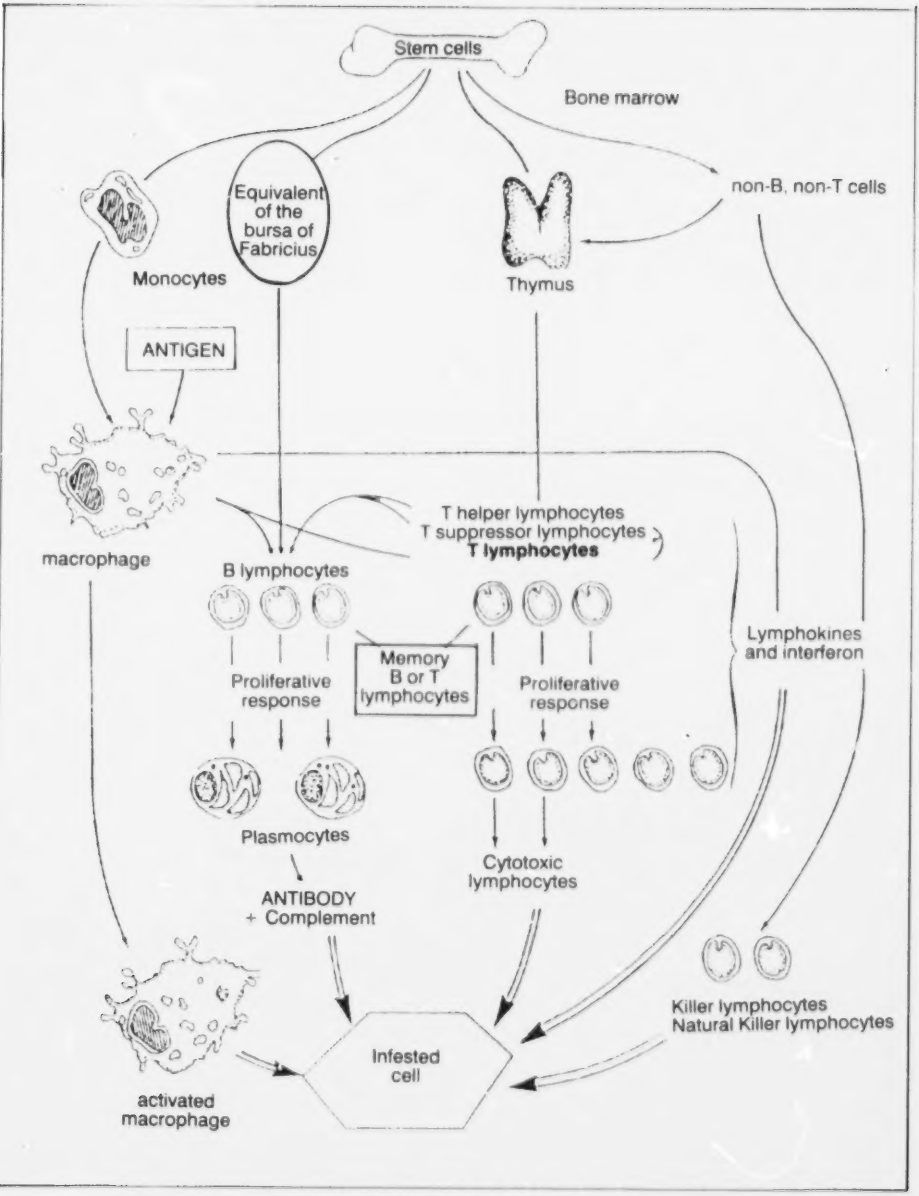

Figure 2 : Different cell populations active in the immune response.

The main facts, then, may be summarized as follows :

When the B lymphocytes are activated (sensitized to the antigen), they proliferate or change into plasmocytes. The sensitized B lymphocytes and the plasmocytes produce large amounts of antibodies specific to the antigen to which they have been sensitized (in other words, antigen-specific antibodies). These antibodies are immunoglobulins.

When the T lymphocytes are activated (sensitized to the antigen), they proliferate. There are several sub-populations, and especially cytotoxic T cells, which attack or destroy, and T cells that produce chemical mediators (soluble proteins known as lymphokines), which act on the different cell populations involved in defending the organism.

Certain B and T lymphocytes called "memory cells" retain the memory of the structure of the antigen.

IUMORAL MMUNITY

In animals, the injection of an antigen causes the development of molecules of protein, or immunoglobulins, which bind specifically to the given antigen. Antibody is the name given to any protein that possesses this ability to specifically recognize a given antigen.

In response to stimulation by a specific antigen, the B lymphocytes proliferate enormously, and change into plasmocytes - which are cells with an intense secretory activity. These sensitized B lymphocytes, and above all the plasmocytes derived from them, secrete immunoglobulins.

mmunoglobulins

Immunoglobulins are divided into five classes, each of which is designated by a letter, preceded by the abbreviation Ig, meaning immunoglobulin. By order of decreasing concentration in the blood, they are : IgG, IgA, IgM, IgD and IgE.

The IgG are most abundant (12 g per litre of blood plasma), and most important in the immune defence mechanisms. It is essential to note that only the IgG cross over from the mother to the foetus, through the placenta, during gestation. Some immunoglobulins also play a major role in protecting newborns and infants during the early months of life.

Each immunoglobulin is composed of four polypeptide chains (protein chains) : two identical heavy chains and two light chains - that is, shorter chains with fewer amino acids, which are also identical for a same molecule of immunoglobulin.

Immunoglobulin molecules are Y-shaped ; this has been amply confirmed by various laboratory techniques (such as electronic microscopy photography using negative staining).

A molecule of immunoglobulin is composed of :

— a constant part, which enables fixation of the complement (see below), and fixation of the immunoglobulin to a receptor,

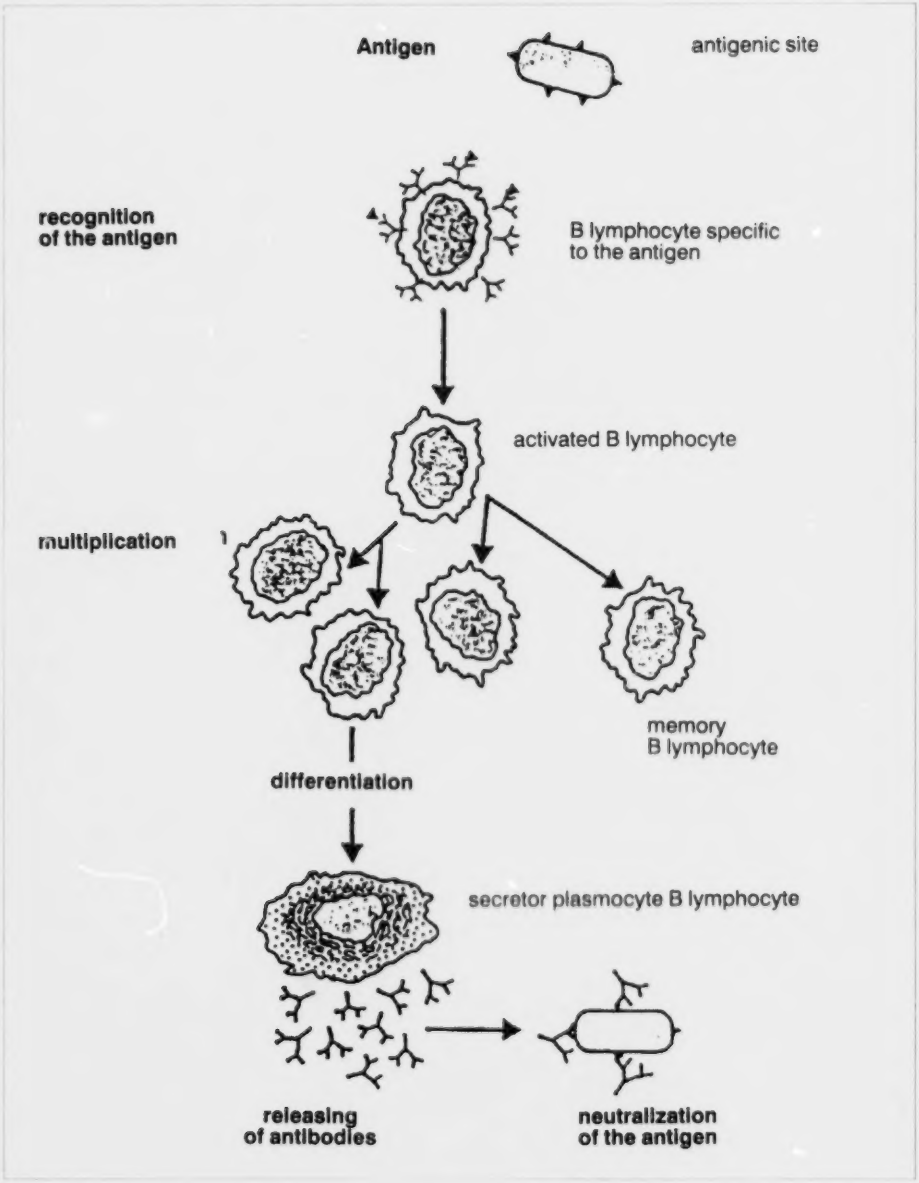

Figure 3 : Humoral immunity
Source : J. ESCALIER, Biologie humaine 3°, Ed. Bordas.

— a variable part. As stated above, our environment contains an enormous, almost infinite number of different antigens. The molecule of immunoglobulin must be capable of accurately recognizing the molecule of a specific antigen. This means that one part of the immunoglobulin must be patterned in such a way as to obtain an extremely precise fit to the shape of one part of the antigen.

It is a fact that descriptions of the structure of immunoglobulin include a variable part (involving hypervariable segments) which differs from one immunoglobulin to another, since it corresponds to a well-defined antigen. The study of genetic determinisms of this variability has stimulated further research.

Although IgG constitutes the largest of the five classes of immunoglobulins, a few words should be said about the other classes.

A immunoglobulin, or IgA, is present in the blood plasma, but also in the exocrine secretions : colostrum and breast milk, saliva, and nasal, bronchial and intestinal secretions. The IgA contained in these secretions combats the penetration of germs through the nasal, bronchial and intestinal mucosa.

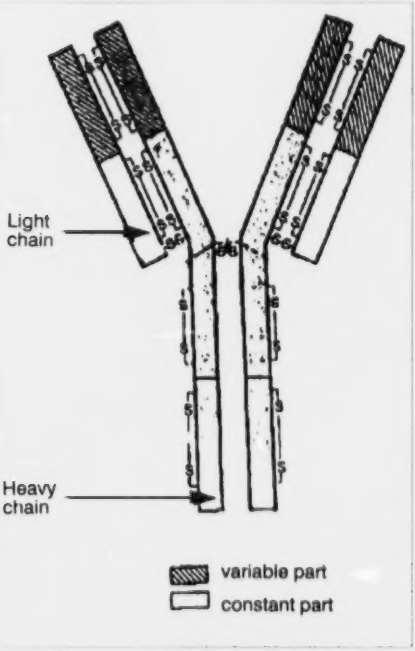

Figure 4 : Structural design of the IgG immunoglobulin. Overall Y shape, two identical heavy chains and two identical light chains. The extremities of the heavy and light chains are composed of "variable" parts capable of fitting themselves exactly to the shape of one portion of the antigen.

Through its presence in colostrum and breast milk, IgA contributes to the protection of newborns and infants against intestinal infections.

IgM develops very rapidly, and participates in the immune response through the activation of complement : these are very large molecules with an agglutinating and cytolytic action.

IgE is involved in allergic reactions (asthma, as well as other signs of allergy), and therefore in anaphylaxis.

As will be seen below, the transformation of B lymphocytes into plasmocytes and the production of immunoglobulins are regulated by certain T lymphocytes. Several of these have a stimulative function, while others control, then terminate action (these are suppressor T lymphocytes) when humoral immunity has worked effectively and is no longer needed.

Applications

The following are some examples of the practical application of scientific understanding of immunoglobulins. It is possible to induce the production of immunoglobulins combating Rh incompatibility. When an Rh-negative mother gives birth to an Rh-positive child, the production of anti-Rh-positive antibodies by the mother's body — a process which may cause adverse effects during subsequent pregnancies — may be avoided by inoculating her with these specific immunoglobulins. This is not yet a common practice in developing countries.

When a woman develops rubella during the second or third month of pregnancy, this otherwise minor disease may be the cause of embryopathy ; that is, it may induce malformations such as congenital cataracts or cardial malformations in the embryo. It is therefore advisable that girls and young women contract rubella or be immunized against the disease before marriage. If this is not the case, and if a 2 or 3 months pregnant woman is in contact with cases of rubella, she may be given injections of specific anti-rubella immunoglobulins. This avoids the risk of foetal malformations.

In other ailments, immunoglobulins obtained from volunteer individuals immunized by several successive injections of an antigen may be given in order to prevent the development of tetanus in a wounded, unvaccinated individual, for instance. These are exceptional solutions, however. It is much simpler to ensure correct vaccination.

Aside from these therapeutic applications, advances in the understanding of immunoglobulins have resulted in some practical applications in the field of biological assay techniques : radioimmune assays, and above all, enzyme-linked immune assays.

Above all, it should be recalled that until Landsteiner's research established the existence of the blood groups, it was not at all possible to perform blood transfusions. These groups are defined by the presence of antigens on the erythrocyte membranes.

If blood is injected into an individual whose blood group differs from that of the donor (to simplify matters, let us consider only the A, B, AB, O group system), the antigens present on the transfused red corpuscles are identified as foreign, and cause the synthesis of antibodies. The ensuing antigen/antibody complex may cause severe, possibly fatal accidents.

Advances in the understanding of humoral immunity and of immunoglobulins has many practical applications, then.

Complement

This term designates a substance composed of some twenty proteins that circulates in the blood plasma and is active, along

with antibodies, in humoral immunity which defends the organism against bacteria and viruses. The different components of this substance are mutually activating, constituting a chain reaction. The most important of these components is C3b.

One of the main roles of complement is the activation of phagocytosis by the polymorphonuclear or macrophage cells.

CELL-MEDIATED IMMUNITY

The first discovery was that when an animal is sensitized to an antigen, it possesses a lymphocyte population (different from the B lymphocytes in charge of synthesizing immunoglobulins) that acts directly on the cells carrying that antigen on their surface.

T lymphocytes

The T lymphocytes originate in the blood marrow like the other cell populations studied in this article. However, the organ by which they are deeply marked and which is essential in that it enables them to attain maturity and immunocompetence is the thymus. It is because of this role of the thymus that they are called T lymphocytes. The thymus, it will be recalled, is an organ located in the upper, anterior portion of the thorax, behind the sternum. Its volume increases during childhood or adolescence, and then gradually declines with age.

The T lymphocytes enter into contact with the thymic cells, after which they may be affected by the action of the thymic hormones, from a distance. One of these hormones, thymulin, is unusual in that it contains zinc (1).

Having acquired immunocompetence with the help of the thymic cells and the hormones produced by the thymus, certain T lymphocytes circulate in the blood, others are stored in the lymphoid organs, ready to be mobilized.

The mechanisms by which the antigen is recognized by the T lymphocytes are complex, and will not be described in the present article.

A classification based on a number of markers defines two groups of T lymphocytes.

The T4 lymphocytes, also known as CD4, are called facilitators, or helpers, since they act on other lymphocyte populations in order to facilitate or amplify their effects.

Many periodicals have published information about T4 lymphocytes in connection with AIDS. It is a fact that the AIDS virus, or HIV, specifically attacks the T4 lymphocytes, and destroys them, thus inducing a dangerous immune deficiency, which is the main characteristic of AIDS. People afflicted with this condition have greatly weakened defences against even the most common infections, precisely because all those defence mechanisms that are dependent on the T4 are deficient.

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(1) See zinc deficiencies (next chapter).

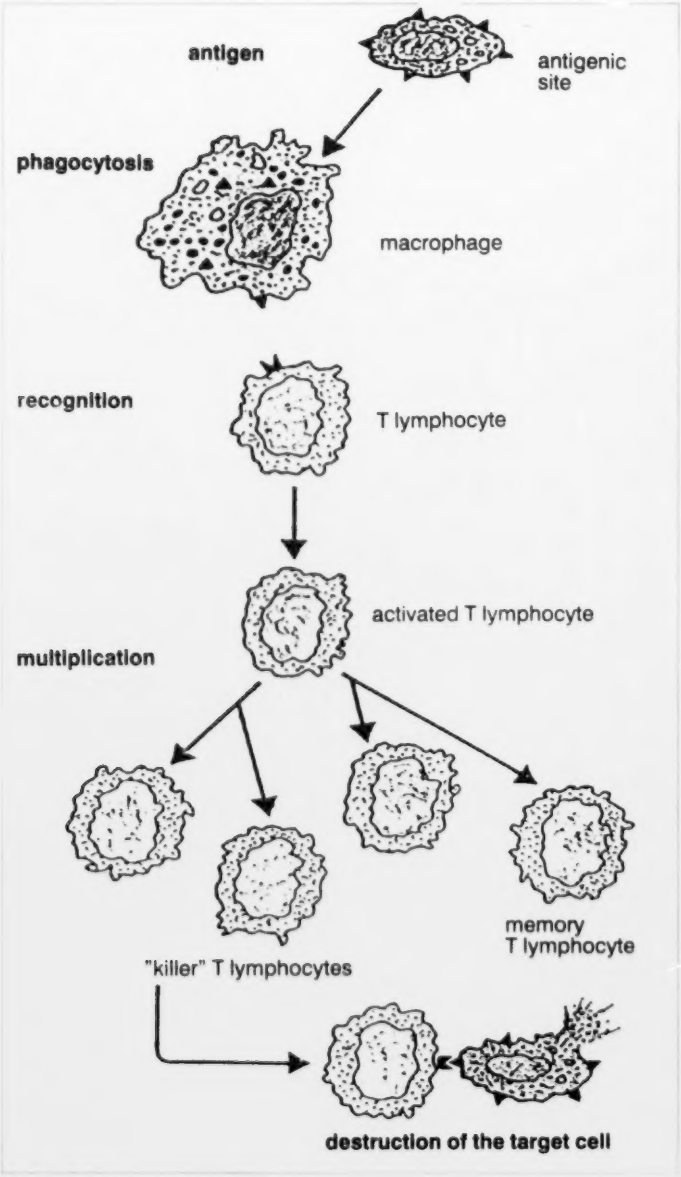

Figure 5 : Cell-mediated immunity

Source : J. ESCALIER, Biologie humaine 3e, Ed. Bordas.

The T8 lymphocytes, also called CD8, some of which are cytotoxic, destroy the cells carrying the antigen to which the lymphocytes have been sensitized. Others have different types of action.

The different sub-groups of lymphocytes may be studied according to their action :

Actions

The "facilitator" or "amplifier" or "helper" T lymphocytes are the T4, which produce chemical messages ; the lymphokines.

Lymphokines are soluble proteins or glycoproteins : over fifty different types have been identified.

Certain lymphokines are active on macrophages, and increase their adherence and phagocytic ability. Others affect the B lymphocytes, so as to stimulate antibody production. There are lymphokines that act on certain sub-groups of T lymphocytes, while others facilitate the synthesis of interferon.

Among these many lymphokines with such varying roles, one of the most important is interleukin 2, also known as "cell growth factor". It is one of a group of molecules that are currently being investigated in connection with growth factors and cell differentiation. It is a fact that when interleukin is bound to a receptor, it results in the active proliferation of any lymphocyte possessing this receptor.

Interleukin

Actually, the action of interleukin 2 is not limited to the T lymphocytes, and more particularly to the cytotoxic T lymphocytes : it also acts on the B lymphocytes, to stimulate the production of immunoglobulins and also on cells which are neither B nor T, but are called NK (Natural killer), and which kill virally induced tumour cells, for example.

Much current research on interleukin 2 is concerned with precisely determining how it may be used for the treatment of infectious diseases, parasitoses and immune deficiencies (of AIDS, in particular) as well as of cancer. It can now be produced by genetic engineering. In 1989, 182 firms specialized in pharmaceutics or biotechnology (including 111 located in the United States) were involved in producing interleukin and determining its therapeutic applications. The other interleukins will not be discussed here.

Once sensitized to an antigen, certain T lymphocytes proliferate and are differentiated into cytotoxic T lymphocytes whose function is to destroy the cells carrying that antigen. They are part of the T8 sub-group. Their action is highly specific : they only destroy those cells that carry the antigen to which they are sensitized, even if there are only a few such cells amidst many others.

The suppressor T lymphocytes put an end to immune responses (in both humoral and cell-mediated immunity) when these are no longer necessary.

Last, there are the memory T cells, which store information on the antigen that triggered off the immune defence mechanisms. If the

same organism is again placed in contact with an identical antigen, the ensuing specific immune response is rapid and intense.

To summarize, T lymphocytes play a role :

— in defending the organism against diseases of bacterial or viral origin ;

— in the rejection or destruction of any body, live or not, identified as "foreign" ;

— in the elimination of those body cells that are no longer normal or are recognized as abnormal. This explains why the incidence of cancer is substantially higher in patients with deficient cell-mediated immunity than in any group of non-immunocompromised individuals.

— in the eventual rejection of grafts when an organ (such as kidney or heart) is transplanted from one individual to another. This is why every attempt is made, before any transplantation, to ensure the best possible compatibility between the donor and the receiver.

IMMUNE RESPONSES TO PARASITIC DISEASES

Responses are highly variable, depending on the parasitosis. In trypanosomiasis, amoebiasis and visceral leishmaniasis, no immunity can be detected. In malaria and schistosomiasis (bilharziasis), an immune responsiveness to the parasite may be observed, but immunity is far from complete. In still other cases, the immune reaction is more efficient, and results in recovery from the parasitic infection : this is the case in cutaneous leishmaniasis.

In parasitic diseases, antigenicity is often highly complex, with each parasite actually representing a mosaic of antigens. There may be different antigens specific to the various phases in the evolution of the parasites. Certain parasites are in constant mutation ; this means that their antigenic characteristics are constantly changing. Parasites induce the production of antibodies within the body, but quite often these antibodies do not afford efficient protection.

As a result of this complex picture, the immune system is less effective in defending the organism against parasitoses than against bacterial infections.

The development of vaccines against parasitic diseases will be much more difficult than for bacterial infections or certain viral infections. However, a number of laboratories are involved in research aimed at the preparation of vaccines against malaria, bilharziasis and other parasitoses.

In conclusion, the immune system in charge of protecting the organism is a highly complex system. It involves a number of cell populations : each of these has some well-defined functions. The

coordination of these and their overall effectiveness are the result of numerous interactions between these different cell populations.

This chapter has painted an extremely simplified picture of the immune system and the mechanisms through which it works. But however cursory, some understanding of the nature of immunity is a necessary prerequisite to any study of the interrelations between nutritional disorders and infection.

INTERACTIONS BETWEEN NUTRITION DISORDERS AND INFECTION

by Henri DUPIN

The immune system may be disturbed by nutrition disorders, malnutrition or specific deficiencies. Furthermore, infection is often an aggravating factor in malnutrition.

Given the bodily defence mechanisms described above, this article will discuss :

— the interactions between protein-energy malnutrition and infection ;

— the effects of certain vitamin deficiencies on immunity : deficiency in vitamin A (retinol), vitamin C (ascorbic acid), vitamin B9 (folic acid), vitamin B6 (pyridoxine) ;

— the effects on immunity of deficiency in certain minerals : zinc, iron.

It is clear that children whose diet is poor, lacking in variety and poorly balanced often suffer from several associated nutritional deficiencies. An understanding of the interactions between nutrition disorders (which disturb the body's immune defences) and infection (which compounds nutrition disorders) yields insight into the need for an extremely broad approach in programmes for the protection of children's health.

PROTEIN-ENERGY MALNUTRITION AND INFECTION IN SMALL CHILDREN

Rates for infantile mortality during the first years of life are still extremely high in most tropical, developing countries. Such high death rates are primarily due to the conjunction of malnutrition and infection. WHO and UNICEF believe this combination — malnutrition/infection — to be responsible for the death of 35,000 children each day.

In many tropical countries, in rural areas as well as in the underprivileged, sprawling suburbs of large cities — zones known as slums, bidonvilles or favelas — from 300 to 400 of every 1,000 live-born children will die before their 4th birthday. This is a dramatic situation, but it should be recalled that a mortality rate of approximately 400 per 1,000 during the first four years of life also prevailed throughout the 17th century and in the early 18th century in France, England and other European countries. This figure was brought down from 400 to less than 20 by the improvement of household and community sanitation, by the fact that infants and small children were given a better diet, as well as by better health monitoring, education for health, routine immunization, the availability of efficient drugs, etc.

In the tropical, developing countries, the mortality figures for small children may be brought down by the active enforcement of simple public health measures — including education on health and

nutrition —, provided this is done with conviction, perseverence and tenacity.

The term "marasmus" is generally utilized when the salient feature in the dietary ration is insufficient energy intake, whereas "kwashiorkor" applies to a dietary imbalance predominantly imputable to a lack of protein ; however, often insufficient calories and protein deficiency go hand in hand. For this reason we speak of protein-energy malnutrition. Deficiencies in minerals (zinc, iron) and vitamins, vitamin C, vitamin B9, vitamin A) are often present simultaneously, since these children's diet is imbalanced and monotonous, as well as wanting in foods of animal origin.

The international organizations (WHO, UNICEF) evaluate the number of moderately or severely malnourished children at 80 to 100 million.

Any discussion of the interaction between malnutrition and infection must deal with two aspects. It is a well-known fact that when infections affect undernourished children they compound this malnutrition and may hasten its evolution. It is equally well known that certain diseases such as measles and staphylococcoses, in particular, are more serious, and entail a greater risk of death, when they affect undernourished children than when they occur children of the same age whose nutritional status is satisfactory.

Infection

These two aspects must be examined, and first, the effect of infection on nutritional status. In underprivileged environments, where poverty and illiteracy prevail, small children often suffer from digestive infections (with common germs, salmonella or enteroviruses), or infections of the respiratory track. These result in loss of appetite, diarrhoea (with hydro-electrolytic losses that are particularly serious for infants and small children, because of the specific features of the metabolism of water at that age), and poor intestinal absorption of food. Further, mothers are convinced that it is best to give the child nothing but herb teas, decoctions of medicinal plants or very light porridges. This type of diet does not cover the child's nutritional requirements.

Infectious conditions are accompanied by an increase in the breakdown of nitrogen. All of these factors have a negative effect on nutritional status. Epidemiological studies have clearly shown that digestive, respiratory and other infections occur in rapid succession in children living in these underprivileged environments. They result in increased malnutrition.

Nutritional Status

Secondly, the consequences of protein-energy malnutrition for the evolution of infections must be analysed. One essential fact is that malnutrition induces thymic involution ; that is, a shrinking of the thymus. As seen in the previous chapter, the thymus plays an essential role in immunity. It is indispensable for the maturation of the T lymphocytes responsible for cell-mediated immunity, which is always disturbed in these cases.

The results of autopsies and of histological testing conducted on children who died of kwashiorkor have shown the volume of

various lymphoid organs to be far below normal ; this is particularly evident in the case of the thymus, which is definitely highly sensitive to protein deficiency, and at the same time is the key organ, immunologically speaking.

In children suffering from malnutrition, and more particularly from kwashiorkor, the number of circulating T lymphocytes and especially of T4 (helper lymphocytes) is lowered, and their maturation is disturbed.

The repercussions on humoral immunity are variable, and published studies on the subject disagree, particularly with respect to secretory IgA. Some researchers have observed a major decrease in immunoglobulins, whereas others find the production of IgG and IgM immunoglobulins to be normal, sometimes even high, with a downward tendency affecting only serum or secretory IgA ; there is also a depression in the C fraction of complement. The vast majority of authors are convinced that even if the mechanisms of humoral immunity are moderately affected, it is legitimate to vaccinate such children against infectious diseases, including measles and pertussis, the occurence of which consistently deteriorates the child's nutritional status.

The interactions between measles and malnutrition (even when the latter is moderate or incipient) are greater and more obvious than for other infectious childhood diseases. Many epidemiological investigations have clearly shown that measles is more serious and more often fatal in undernourished children than in those whose nutritional status is satisfactory. Undernourished children also tend to have more severe cases of staphyloccoses (cutaneous, pulmonary or other) than well-nourished children.

While the course of some other infectious diseases is not affected by nutritional status, conversely, these diseases do have repercussions on nutritional status, if only because they cause loss of appetite, digestive disorders and fever.

MALNUTRITION AND INFECTION IN MATURE AND ELDERLY PEOPLE

Many studies conducted in the belligerent countries during the first and second world wars, or more recently in a number of tropical countries, supply evidence of an increase in tuberculosis-related morbidity and mortality during periods of famine.

Other studies, also conducted during wars or in developing countries, have shown that typhus fever (a disease caused by Rickettsias) is much more severe in undernourished or malnourished individuals than in those with a satisfactory nutritional status.

It is a known fact that during the first days following surgery, infections occur more frequently and are more serious in undernourished individuals than in those whose nutritional status is good.

One particularly serious problem continues to prevail in many tropical and subtropical countries : the problem of women who

have had repeated pregnancies and periods of lactation, whose work is very tiring and whose dietary regimen is inadequate — because of the climate or for social and economic reasons —, women whose nutritional status is often deficient. For them, as for young children, the consequences of the interactions between a poor nutritional status and infection are most serious. Only a very broad conception of prevention (including planned parenthood, the improvement of nutritional status, hygiene and sanitation, and the early treatment of infection) would be susceptible of improving this situation.

EFFECTS OF CERTAIN VITAMIN DEFICIENCIES ON IMMUNITY

VITAMIN A DEFICIENCY

Vitamin A deficiency is extremely frequent, especially in small children, in Indonesia, India, Bangladesh, Haiti and some parts of Latin America, but it is also present in North Africa and sahelian Africa.

Emphasis has rightly been placed essentially on the ocular damage caused by vitamin A deficiency, since close to 500,000 children are affected by this condition each year, and one third of them are blinded. However, this deficiency has other serious consequences, owing to its repercussions on immunity : these involve the increased frequency and severity of infections.

It should be recalled that the human diet supplies both vitamin A (the biochemical name of which is retinol) and provitamin A (which is transformed into active forms within the body). Retinol is only present in foods of animal origin (fish, fish liver oil, the liver of mammals, milk, butter). Certain plant foods such as palm oil, mangoes, papayas and leafy green vegetables are particularly rich in provitamins (beta-carotene).

The reason why small children are the main victims of vitamin A deficiency is that they are not given a varied, diversified diet at a sufficiently early age.

Vitamin A has a number of functions. It is essential for good eyesight, since it is necessary for the synthesis of visual pigment in the retinal cells ; one of the first signs of deficiency is a decline in vision when light is low, for instance at dawn and at twilight.

Vitamin A regulates the multiplication and the differentiation of epithelial cells ; it is responsible for maintaining the different types of epitheliums (corneal epithelium, bronchial and bronchiolar epithelium, etc.) in satisfactory condition.

It is active in the enzymal processes that enable the body to metabolize foreign substances and to eliminate toxic substances. Last, and this is the point with which we are concerned here, vitamin A plays a major role in the immune mechanisms.

Infections have repercussions on the vitamin A status. In regions where vitamin A deficiency is highly endemic (Indonesia, India, Near East, central America), epidemiological studies have shown that in small children the clinical signs of deficiency (affecting the eyes : the conjunctiva, then the cornea) quite often occur in

conjunction with a bout of infection, of measles or of viral hepatitis. The vitamin A deficiency actually pre-existed, but was only revealed by biological testing. The occurrence of a severe infection suddenly increased the deficiency, causing the development of the characteristic ocular signs.

Vitamin A plays a role in the immune mechanisms, but little is known as yet of how it works ; the epithelial damage is only one aspect of the question, and definitely not the most important one. In any case, experimental studies on animals confirm and substantiate observations made on human patients : vitamin A-deficient animals are much more sensitive to disease than non-deficient animals.

VITAMIN C DEFICIENCY

The history-making reports on scurvy among sailors mentioned greatly enhanced sensitivity to infection, in addition to deterioration of the gums, bleeding and increased fatigability.

Experimental studies conducted on those animal species which, like human beings, are unable to synthesize ascorbic acid (guinea pigs, primates), have shown that vitamin C-deficient animals are more sensitive to pneumococci, streptococci, salmonellas, rickettsias, etc...than control animals.

Furthermore, in humans, infectious diseases have been proved to be connected with a lowered seric ascorbic acid concentrations. Some experimental investigations of healthy individuals tend to indicate that a satisfactory dietary intake of vitamin C increases the circulating IgA and IgM immunoglobulin levels, enhances the mobility and activity of leukocytes, stimulates the transformation of lymphocytes and favours the production of one component of complement : the C3 factor.

Vitamin C (ascorbic acid) participates in a variety of ways in the proper functioning of immune reactions, then.

As everyone knows, vitamin C is found essentially in fresh fruit. Certain vegetables and leaves are rich in vitamin C, but much of it is destroyed when heated, and especially by extended cooking.

FOLATE DEFICIENCY

Folic acid is a vitamin in the B group. It is sometimes designated as vitamin B9. When contained in food it takes the form of folates ; the active form is tetrahydro-folic acid, which plays a role in many of the body's metabolic reactions, and especially in connection with many enzymes.

The role

This vitamin is necessary for the synthesis of the bases that are an element in the composition of nucleic acids. It should be recalled that the nucleic acids constitute the material on which all genetic information characterizing a given individual is inscribed ; that is, all of the individual's genes. They also make up the ribonucleic acids, or RNA ; that is, the molecules which receive coded messages and enable the transcription of these messages and the synthesis of proteins. The organism of any child or adult possesses some 60,000 different proteins, some present in great quantities, others in smaller amounts, but all of which are constantly

being renewed ; the pace at which each type of protein is renewed is controlled and regulated with great accuracy.

Folic acid deficiency affects cell division ; its repercussions are particularly evident on cells with a rapid turnover, such as the cells composing the intestinal mucosa, and even more, the blood cells. Every day, the human body synthesizes about one hundred billion new red blood corpuscles and destroys an equivalent number. Each day, too, fifty billion intestinal cells are renewed. These figures may come as a surprise, but there is no printer's mistake here, we are really talking in terms of billions.

A folic acid deficiency, then, affects the sythesis of those cells that are active in the immune mechanisms. What disturbances of the immune defence system are observed in case of folic acid deficiency ?

As in iron deficiency, humoral immunity is less disturbed than cell-mediated immunity. Experimental studies on animals have shown that a folic acid deficiency results in atrophy of the thymus which, as seen above, is a gland with an all-important role in the maturation of the T lymphocytes. The latter achieve their immunocompetence through the action of the thymic hormones.

In severe folic acid deficiencies in laboratory animals, the weight of the thymus decreases, with a concomitant decrease in the number of thymic cells. This in turn affects the number and maturation of the T lymphocytes. These disturbances may be corrected by the administration of folic acid.

The pathology seen in animals with experimentally provoked folic acid deficiency is also observed — but more discretely, of course — in children and adults with this vitamin deficiency. More specifically, they are found to suffer from disturbed cell-mediated immunity, and especially from a decreased number of T lymphocytes, above all of T4. Lymphocyte response to solicitation by antigens is abated. Skin tests designed to study retarded hypersensitivity dependent on cell-mediated immunity are disturbed as well.

In practice, folate deficiencies are very often seen in conjunction with iron deficiency in children, and even more clearly so in pregnant women. For this reason, public health programmes whose objective is to combat these two deficiencies (which are both factors in anaemia), associate iron and folates.

Pyridoxine deficiency has deepseated repercussions on the immune functions, both on cell-mediated immunity and on humoral immunity (production of immunoglobulins).

EFFECTS ON IMMUNITY OF DEFICIENCIES IN SOME MINERALS

ZINC DEFICIENCY

Zinc deficiency owing to insufficient dietary intake was first reported in 1961, by Prasad, in Iran, then by others in Egypt, and subsequently in many developing countries. Insufficient dietary zinc intake is frequently associated with malabsorption problems.

Infantile protein-energy malnutrition (PEM) may be of several types, involving insufficient energy intake, insufficient protein intake and/or deficiency in various vitamins and some minerals, including zinc. In addition, the drop in serum albumin concentrations in the course of these conditions (a major biochemical feature in PEM) decreases zinc transport to the body's cells, since the zinc contained in the blood is normally bound to albumin.

In children as in adults, diets with a high plant fibre content and a high phytate concentration considerably diminish the absorption of zinc as well as of some other minerals of dietary origin. This is a contributive factor in deficiency. In adults, alcohol abuse definitely increases zinc deficiency.

There is a congenital disease, enteropathic acrodermatitis, which is apparently caused by a congenital lack of one of the enzymes involved in zinc absorption. This disease is extremely rare, however, and will not be discussed here.

Another far more important public health problem is the zinc deficiency frequently observed in children with drepanocytosis.

The body only contains minimal amounts of zinc : adults only possess 2 or 3 grammes. Despite the smallness of this quantity, zinc fulfills some essential biological functions : it is active in a great many enzyme systems (more than 70) ; it is indispensable to height growth in children, and subsequently to their puberal maturation. Zinc is also indispensable in the development of immune defences in the young organism.

The thymus is seen to atrophy in case of zinc deficiency. When laboratory animals are deprived of zinc, atrophy of the thymus is noted, along with severe disturbances of the synthesis and maturation of the T lymphocytes, which of course then leads to greater vulnerability to infection. As shown above, the maturation of these T lymphocytes first involves direct contact between the lymphocytes and the thymus, after which it continues outside of this organ, but with the help of special hormones produced by the thymus. The presence of zinc is required in order for one of these, thymulin, to fulfill its function, which is to enable the T lymphocytes to achieve immunocompetence.

The role of zinc

The role of zinc in immunity is not only contingent on the fact that its presence is necessary for the action of thymulin, but also on the fact that the participation of zinc is required for the activity of several chemical messengers (lymphokines) produced by the T lymphocytes in order to stimulate the various cell populations involved in the body's immune defences.

When a child suffers from zinc deficiency, a lowered blood concentration of thymulin is observed (when laboratory assay can be performed) along with disordered maturation of the T lymphocy-

tes. As a result of this disturbance, disorders occur in the immune defences, including a decrease in the production of IgG and IgM antibodies in response to solicitation by an antigen. The frequency and severity of bacterial infections are therefore increased in zinc-deficient children. Immune disorders may subside when children or adolescents are given supplementary doses of zinc.

It is essential to keep in mind that while isolated zinc deficiency has been discussed here, multiple deficiencies involving proteins, various vitamins, iron and zinc are infinitely more frequent in everyday medical practice than isolated deficiencies.

The objective is not the treatment of pathology but its prevention. A varied, diversified diet, sufficiently rich in foods of animal origin (meat, fish, eggs, dairy products) is necessary at all ages, but especially for small children whose nutritional requirements are particularly high because they are growing rapidly. The zinc is easier to digest when it is contained in foods of animal origin than in plant foods.

IRON DEFICIENCY

Iron deficiencies are extremely frequent, especially in what are known as the developing countries. According to WHO, they are the most widespread of all deficiencies, world wide, and affect approximately 700 million individuals. "Children in the Tropics" has devoted two issues, both written by Dr. S. Hercberg, to nutritional anaemias (n° 133 in 1981 and n° 186 in 1990).

In 1985, E.M. Demayer and M. Adiels-Tegman published an overall study of the prevalence of anaemia, grouping the findings of 472 surveys or limited studies conducted in 110 countries (The prevalence of anemia in the world. WHO, 1985). At that time, according to this document, anaemia, generally involving iron deficiency, affected 51 % of children under 4 years old, 46 % of 5 to 12 year-olds, 47 % of menstruating women, 26 % of adult men and 59 % of pregnant women in developing countries, with considerable inter-country differences.

A recent study implemented by S. Hercberg et al in southern Benin concentrated on iron deficiencies, specifically, with a distinction between those that had not yet reached the stage of anaemia, and those that had reached this stage. The overall findings are shown below.

For a number of reasons, including their repercussions on the body's defence mechanisms (those involved in immunity), iron deficiencies represent a major public health problem, particularly in developing countries.

Table 1 :
IRON DEFICIENCIES

Population groups	Iron deficiency, defined by blood ferritin < 12 µg/l, along with a percentage of transferrin saturation < 15 %	Iron-deficiency anaemia (based on WHO reference values)
Infants, 6 to 24 months	62,2 %	52,2 %
Children, 25 to 72 months	30,2 %	24,0 %
Children, 6 to 14 years	27,6 %	21,9 %
Menstruating women	34,3 %	20,6 %
Adult men	12,0 %	5,9 %

Source : S. HERCBERG et al, Public Health. 1988, 102, pp. 73-83.

Supplementation

In past years, the relations between iron deficiency and resistance to infection have been the object of contrasting interpretations. Some authors contended that iron deficiency is conducive to infection and that the administration of iron supplements to deficient individuals would enhance their resistance. Others felt that iron supplementation might be harmful : research has shown that a great many micro-organisms need iron in a free state (not bound to proteins) in order to proliferate, and additional intake of iron would therefore enable bacteria to multiply. This would be particularly the case in iron-deficient neonates and infants given large amounts of iron. In fact, supplementation does not contribute to germ development unless large quantities of iron, exceeding the binding capacity of transferrin, are provided : the iron that is not bound to proteins, and is therefore present in a free state, is then available for use by micro-organisms. Many enzyme systems, and especially the cytochromes, catalases and peroxidases, are known to contain iron. It has recently been discovered that even a moderate iron deficiency has repercussions on these leukocytic enzyme systems, and this then lowers the body's resistance to infection.

Several epidemiological and clinical studies have uncovered the high incidence of infections in iron-deficient individuals and — most important — the fact that this incidence decreases when these groups are given iron supplements.

Research investigating the relations between iron status and immunity in children is often difficult to interpret, since iron deficiency in children, even more than in adults, tends to be associated with other nutrition disorders such as protein-energy malnutrition and zinc or vitamin deficiencies. Further, certain authors did not use indicators that were sufficiently specific or reliable for the accurate definition of iron status or for the analysis of disturbances in immunity. Despite these difficulties, sufficient information is now available, since observations of adults and children have been completed by experiments on laboratory animals.

Some facts have now been established :
— iron deficiency affects the body's immune defences ;
— it influences cell-mediated immunity more than humoral immunity ;
— iron-deficient individuals, like laboratory animals fed a diet lacking in iron, show a decrease in the number of circulating T lymphocytes ;
— lymphocyte proliferation in response to an antigen is lower in iron-deficient individuals than in those with no deficiency ;
— the ability of macrophages to destroy bacteria is decreased ;
— in severe cases of deficiency, the production of antibodies (humoral immunity) is moderately diminished.

One important fact must be stressed : if sufficient amounts of iron are provided these anomalies rapidly disappear. This has been observed both in iron-deficient children and adults and in experiments on animals. Such therapeutic testing corroborates the fact that the anomalies seen are definitely connected with iron deficiency.

The production of antibodies subsequent to vaccination should be mentioned here. Experimental research has shown that vaccination of animals with severe iron deficiency results in the production of smaller amounts of antibodies (immunoglobulins).

In 1975, however, Chandra and Saraya demonstrated that the antibody rates induced in children in response to tetanus vaccination were practically the same, irrespective of whether or not the children suffered from an iron deficiency.

As mentioned earlier, humoral immunity (the production of antibodies in response to antigenic stimulation) is definitely less affected by iron deficiency than cell-mediated immunity. This means that children with moderate iron deficiency may be vaccinated against infectious diseases.

In 1989, the CRAN (Centre for Research on Nutritional Anaemia) and the ORSTOM undertook a longitudinal investigation of children in Togo. The object of this study was to accurately determine the

effects of iron supplementation. To do so, a double blind method was used : some children were given iron tablets at regular intervals, while others were given placebo tablets.

This study is still under way, but it has already shown that the percentages of T lymphocytes (taken as a whole) and of helper T lymphocytes are lower in iron-deficient children than in those with no such deficiency. It was also noted that digestive, rhinopharyngeal and respiratory infections were more frequent in iron-deficient children than in non-deficient children.

For the prevention of iron deficiency, it is essential to combat those diseases (ancylostomiasis, for instance) that result in increased losses of iron, and to make sure that everyone, including small children, benefits from a varied, diversified diet.

It should be emphasized that the haeme iron present in meat is much more easily digested than non-haeme iron : women, and especially pregnant women, should therefore receive at least as large a portion of meat as men. The gradual diversification of infant diets is preferable, with the introduction of meat, cut into tiny pieces or chopped, starting at age 10 months.

ALCOHOL ABUSE AND IMMUNITY

This text is mainly concerned with children, but some questions pertaining to adults have been briefly discussed. Although it deals with nutrition disorders caused by insufficient dietary intakes, some mention will be made of alcohol abuse, which is the excessive consumption of alcoholic beverages. It is the cause of nutrition disorders, through a number of mechanisms :

— some are directly connected with the consumption of alcoholic beverages. As soon as the acceptable dose is exceeded, alcohol has a toxic effect on different organs, and especially on the liver and the nervous system ;

— others are linked with social behaviour and an extremely imbalanced diet ;

— still others are the result of metabolic disturbances caused by alcohol.

Alcohol abusers — with or without cirrhosis — tend to suffer from bacterial infections more frequently and more seriously than non-abusers of the same age. These infections, caused by streptococci, pneumococci, enterobacteria or other infectious agents, frequently have a more protracted course in alcohol abusers, and are more difficult to cure than in the overall population.

Chronic abusers frequently develop hypergammaglobulinaemia with high IgM and more importantly high secretory IgA concentrations. Leukopenia (a lowered number of circulating white corpuscles) and above all lymphopenia are often observed in chronic alcohol abusers.

Several studies place special emphasis on the diminished number of circulating T lymphocytes. Experimental studies on animals have corroborated the existence of disturbances in tests used to study cell-mediated immunity. In laboratory animals subjected to the action of alcohol (by inhalation or injection of alcohol), the mobilization of leukocytes and their migration to the sites of infection are seen to be defective, and their chemotaxis is impaired. All this makes the leukocytes less efficient in combating any pathogenic germs.

In short, chronic alcohol abusers may be said to show increased susceptibility and vulnerability to infection. In addition, chronic alcoholism is a systemic disease affecting several organs including the liver and the nervous system.

Chronic alcohol abusers often have a poorly balanced diet : ethanol (alcohol) represents a major portion of their energy intakes ; there is frequently an insufficient intake of proteins, and especially of certain indispensable amino acids, as well as a deficit in the intake or utilization of several vitamins (B1, B2, B6, niacin, folic acid) and some minerals. These deficiencies may be disrupting factors in the immune mechanisms.

Conclusion

Infections may contribute to impairing nutritional status or they may worsen incipient malnutrition. This is particularly true in small children. At the same time, nutrition disorders may disturb the immune mechanisms, making individuals more vulnerable to various infections.

For those groups at greatest risk, individual, curative medical practices remain relatively ineffective in solving these problems. An overall approach (a public health policy) is required so as to limit the dissemination of infection and to prevent deficiencies or dietary imbalances.

IMMUNITY AND VACCINATION

by Nicole GUERIN

IMMUNOGLOBULINS IN THE FOETUS AND NEONATE

At birth, children possess the immunoglobulins that were transmitted to them transplacentally by their mother, as well as those produced by their own immune system. The evolution of these is shown in figure 6.

The foetus is capable of producing certain classes of antibodies at a relatively early age : immunoglobulins of the IgG type may be developed at ten weeks of intrauterine life, and IgM at twelve weeks. It is unable to synthesize IgA, IgD and IgE, on the other hand. Complement synthesis begins at the eighth week of foetal life, thus preceding immunoglobulins. However, it is only after twelve to fourteen weeks of gestation that large amounts are produced.

The IgG are the only maternal immunoglobulins that are capable of actively crossing the placenta. This transmission is moderate during the first six months of pregnancy, and only takes on considerable proportions during the last three months. This change is attributed to a sudden increase in placental permeability. The neonate's humoral immunity is essentially dependent on the transmission of passive immunity from mother to child, through active, transmembranal transfer across the placenta.

The immunoglobulins present in the neonatal circulation (in the cord blood, for instance) are mostly IgG of maternal origin. In

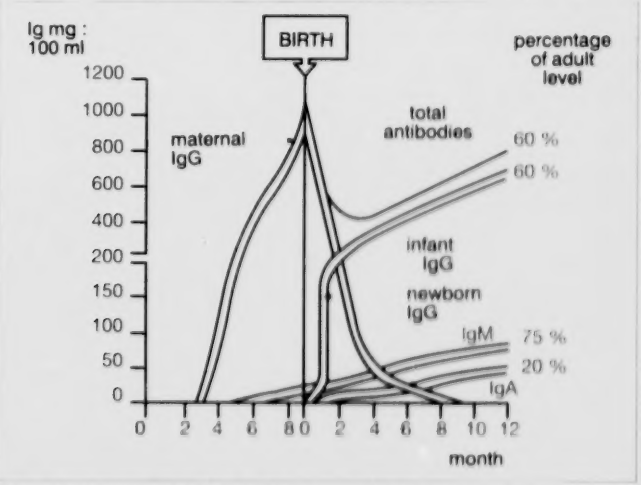

Figure 6 : Immunoglobulins in the serum of the foetus and newborn child. IgG in the foetus and newborn infant is derived solely from the mother. This maternal IgG has disappeared by the age of 9 months, when the child is synthesizing its own IgG. The neonate produces its own IgM and IgA ; these classes cannot cross the placenta. By the age of 12 months, the infant produces 60 % of its adult level of IgG, 75 % of its adult IgM level and 20 % of its adult IgA level.

Source : I. ROITT, J. BROSTOFF, D. MALE et al, Immunology, New York, Grover Medical Publishing, 1989, chapter 14, page 9.

at-term neonates, their concentration is generally equal to or slightly higher than that of their mother. This is because the placenta is capable not only of passive transmission, which would explain identical concentrations in mother and child : it may be capable of concentrating the antibodies, thus causing the surprising fact of a higher concentration in the child than in the mother.

These immunoglobulins are mostly composed of antibacterial and antiviral antibodies, which play a major role in protecting the infant during the first six months of life. This explains why infants usually retain protection against measles and poliomyelitis for several weeks. These antibodies then subside more or less rapidly, and the time elapsed before they disappear depends on a number of factors such as their initial concentration and the nature of the antibodies.

The mother can only transmit those antibodies that she possesses. A mother who has had measles may transmit antibodies against measles to her child ; the more recent her illness, the higher the concentration will be. Similarly, a mother who has been vaccinated against poliomyelitis will transmit those antibodies to her child, just like a mother who has been vaccinated against tetanus. The infant's serum antibody concentration will be higher when its mother has been more recently and more completely immunized.

A mother who has been recently immunized against tetanus will transmit higher concentrations to her child than one who was vaccinated ten years earlier : a child born to the former does not run a risk of contracting neonatal tetanus, whereas the offspring of the latter is not protected.

Conversely, if the mother has not been vaccinated at all, or has not been infected by measles or poliomyelitis, she will not transmit any specific antibodies to her newborn baby, who may then catch these diseases at a very early age. This explains some extremely precocious cases of these infectious diseases. Such cases, which are relatively rare, always come as a surprise, since most of these mothers are completely unaware that they never contracted measles, not to mention the fact that they were never infected by the poliomyelitis virus, since 999 out of one thousand such infections go unnoticed.

The presence of maternal antibodies is not entirely beneficial, however : these transmitted antibodies may inhibit the immune processes induced by vaccination. For this reason, vaccination against measles is usually recommended at age nine months. When performed at an earlier age it is only partially effective ; it is a failure in one out of two cases when administered at age six months. This is explained by the presence of maternal antibodies which inhibit the child's immune response, and do so all the more effectively when the child is younger ; that is, when the concentration of passively transmitted antibodies is higher.

To counter the influence of maternal antibodies, highly antigenic vaccines must be used. Such is the case of the tetanus vaccine, for

instance, which is effective in six week-olds. The new, highly concentrated measles vaccine strains — the Edmonston-Zagreb or AIK-C — may also be used when the prevention of measles in children under nine months old is essential because of a high epidemiological risk, such as it exists on the underprivileged periphery of urban centres.

Last, the specific antibodies that afford protection against certain diseases are unable to cross the placental barrier, either because they are too complex or because the molecules of which they are composed are too large.

No transmitted anti-pertussis antibodies are found in the neonatal blood, and for this reason the disease may be caught by the neonatal at any time, from birth on.

The cell-mediated immunity triggered by the BCG to afford protection against tuberculosis is not transmitted from mother to child either. This is why contamination with the tubercle bacillus, the vector of tuberculosis, is possible immediately after birth.

BCG vaccination can and should be performed during the first days of life.

The immunization schedule is conditioned by variations of this type. Certain highly antigenic, extremely "strong" vaccines are practically not destroyed by the transmitted antibodies. This is the case of toxoid-based vaccinal preparations, such as the tetanus vaccine. Others, on the contrary, and especially the live attenuated vaccines, and most importantly the conventional measles vaccine, are particularly sensitive to the presence of circulating antibodies.

Table 2 :
CLASSIFICATION OF VACCINES

NAME	TYPE	IMMUNITY INVOLVED
BCG	Live bacterial	Cell-mediated
Pertussis	Killed bacterial	Humoral mediation
Conventional typhoid	Killed bacterial	Humoral mediation
Cholera	Killed bacterial	Humoral mediation
Meningitis CS	Bacterial polysaccharaide	Humoral mediation
Pneumococcal	Bacterial polysaccharaide	Humoral mediation
Typhoid VI	Bacterial polysaccharaide	Humoral mediation
Diphtheria	Toxoid	Humoral mediation
Tetanus	Toxoid	Humoral mediation
Oral poliomyelitis	Attenuated virus	Humoral and local mediation
Measles	Attenuated virus	Humoral and cell mediation
Rubella	Attenuated virus	Humoral mediation
Mumps	Attenuated virus	Humoral mediation
Yellow fever	Attenuated virus	Humoral mediation
Influenza	Inactivated whole virus	Humoral mediation
Injectable polio	Inactivated whole virus	Humoral mediation
Rabies	Inactivated whole virus	Humoral mediation
Hepatitis B	Inactivated viral antigen fraction	Humoral mediation

Table 2 lists a number of vaccines, showing their type and the classically described immune mechanisms on which their action rests.

VACCINATION OF PREMATURES

The immune system of prematures is not very different from that of full-term infants. Comparative serological studies have been conducted on full-term infants and prematures with a gestational age of less than 37 weeks. They have shown that the administration of 3 doses of a combined triple diphtheria-tetanus-pertussis vaccine — that is, the complete conventional immunization scheme — produces identical antibody levels in the two groups of children.

This study corroborates the usual recommendations for vaccination of prematures in accordance with their chronological age rather than with their gestational age.

IMMUNE RESPONSE IN IMMUNOCOMPROMISED CHILDREN

Children with congenital or acquired immune deficiency have unusual responses to vaccination.

Children undergoing immunosuppressive treatment should not be given any vaccine containing a live attenuated virus. However, under some extremely specific circumstances it is possible to perform vaccination, provided a number of precautions are taken : the treatment must be suspended at least three months prior to immunization, and for another three to twelve months after it. Trial anti-tetanus and diphtheria immunization has proved to be slightly less effective — in terms of the antibody response elicited — in children undergoing immunosuppressive treatment than in normal control individuals. Lowered responses have also been observed following immunization against influenza.

VACCINATION OF CHILDREN BORN TO MOTHERS INFECTED BY THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

It is a known fact that 25 to 30 % of mothers infected by the HIV transmit the infection to their child during their pregnancy. The question of whether or not to vaccinate these children has therefore been debated : is vaccination dangerous in these infected children ? Is vaccination effective in such children ?

In the present state of findings, the tentative conclusions are as follows :

— killed bacterial or viral vaccines and toxoids are effective and the antibody levels elicited in this type of vaccinee are comparable to those seen in children born to uninfected mothers.

— live viral vaccines such as the measles and smallpox vaccines may also be administered to these children. The risks of complication in case of measles disease — to take this example — are so great that they substantially outweigh any potential risk connected with vaccination. Immune responses are sufficiently adequate to afford valid protection.

— the BCG, the only live bacterial vaccine, does not seem to generate any more frequent local or systemic complications when administered to children born to HIV-infected mothers. When the incidence of tuberculosis is high, vaccination is therefore recommended. It is disadvised, however, when the child personally shows clinical signs of AIDS.

IMMUNE RESPONSE IN MALNUTRITION AND DEFICIENCY

Does malnutrition modify responses to vaccination ? This is the question of the effectiveness of immunization in malnourished individuals.

There are two ways of evaluating responses to vaccination : in the laboratory or in the field. Laboratory testing involves quantitation of the specific circulating antibodies induced by a given vaccination. In field work, the protective capacity of a vaccine — that is, its ability to prevent a person from falling ill following contact with germs of that specific disease — is determined. Few studies of this type have been conducted on persons suffering from malnutrition.

Serological testing yields varying results depending on the vaccine. These are summarized below.

Immunization against measles

Some authors find low antibody levels in malnourished individuals, while others report a delayed development of antibodies. Still others do not observe any difference correlated with nutritional status.

Immunization against tetanus and diphtheria

Here too, studies tend to differ somewhat. Some authors find a slightly weaker response in malnourished individuals, whereas others record absolutely identical responses. Apparently the insufficient reactions are seen on mid-course assays, before completion of the full course of vaccination, since children who had received all of the doses required for protection developed similar responses irrespective of their nutritional status.

Immunization against pertussis

No study of the effects of this vaccination on malnourished individuals is available.

Immunization against poliomyelitis

Insufficient antibody responses following immunization against poliomyelitis using the Sabin type oral attenuated vaccine can hardly be imputed to malnutrition alone. A number of factors may be involved in failure, some of which are the competition with other enteroviruses and the vaccine's thermolability. However, a low secretory IgA concentration has been observed in malnourished children subsequently to oral vaccination.

Immunization against yellow fever

This vaccine has only been studied once, in 1964, using a small group of children : the outcome was disappointing. Actually, when epidemics occur, everyone is vaccinated, including the malnourished.

Immunization against hepatitis B

A Kenyan study did not find any difference in response between malnourished and healthy children.

There hardly seems to be any difference in immune responses to vaccination, then, in children suffering from nutritional deficiencies. Humoral responses generally remain intact, as shown in the previous chapters. They are only impaired to the extent that the antibody response calls on the macrophage-T lymphocyte couple. There is no negative effect on secondary responses.

Immunization with the BCG

Cell-mediated reactions are diminished, owing to the thymic involution generated by malnutrition. The BCG is particularly well known to be less effective when administered to a malnourished

child. However, the method conventionally used to evaluate the BCG — post-vaccinal tuberculin seroconversion — is also modified by the decreased volume of the thymus ; as a result, only comparative epidemiological studies of the protection afforded by the BCG in normal and malnourished children may provide an answer to the question : is the BCG effective in malnourished individuals ?

Malnutrition usually develops after weaning. It is recommended that all vaccinations be administered before that time, both because of this and for epidemiological reasons : immune responses are more satisfactory, and the period of exposure to the risk of contracting the disease is reduced. It should be noted that no increase in the frequency or severity of adverse reactions has ever been observed following the administration of vaccines to malnourished children.

Vitamin A and iodine deficiencies

Vitamin A deficiency causes blindness in 250,000 children around the world each year. It doubles and sometimes even triples the morbidity rate for acute respiratory infections and diarrhoea in high-risk areas. It is associated with a decreased survival rate in children.

Figure 7 : "Don't forget to vaccinate my mom too ! "

Source : EPI Update : Neonatal Tetanus, WHO, Sept. 1988.

While the harmful effects of vitamin A deficiency on resistance to infections is well known, little is known of its consequences with respect to immune response to vaccinations.

Iodine deficiency is at the origin of cases of goitre and deaf-and-dumbness, as well as of increased perinatal and infantile mortality. Its most serious consequences are cretinism, which affects three million individuals, deaf-and-dumbness and mental deficiency.

However, no immunological investigation has been conducted on these children so far, and there is no information on whether or not this deficiency modifies their antibody responses. There does not seem to be any major difference in their degree of protection against disease. As for iron deficiency, the previous chapter shows that it does not modify immune responses to tetanus vaccination.

IMMUNIZATION OF MOTHERS

Women, and especially mothers and expectant mothers often experience considerable nutritional deficits. These include general malnutrition or multiple deficits including iron-deficiency anaemia and/or vitamin B12 deficiency. When they are in need of vaccinations, these should be administered cautiously, and with full knowledge of the facts.

Like all adults, mothers have generally been subjected to infection by the measles and poliomyelitis viruses during childhood. Vaccinations against these diseases are therefore no longer of any use to them, no more than immunization against pertussis and diphtheria ; at the most, booster injections against certain diseases may be given for stays in endemic areas. If necessary, mothers may be immunized against hepatitis B, cerebrospinal meningitis A or C, and influenza.

Some other vaccines, essentially those based on live, attenuated viruses, are strongly proscribed, on the other hand, owing to the teratogenic risks incurred by the foetus. The only exception is immunization against yellow fever in case of an epidemic : all women, including expectant mothers, should be vaccinated if an epidemic threatens.

Immunization against rabies is necessary when a pregnant woman is bitten by a rabid or suspectedly rabid animal. Indeed, rabies is a 100 % lethal disease, and vaccination is necessary despite the risk of adverse reactions.

The importance for children of receiving transplacentally transmitted maternal antibodies, especially for protection against neonatal tetanus, has been thoroughly discussed above. During their pregnancy, women are capable of responding to antigenic solicitation such as that offered by tetanus vaccination. This is one way of combating the terrible threat represented by neonatal tetanus, which takes an annual toll of some 800,000 lives. Immunization is one element in the fight to control this disease, which mainly requires the improvement of the sanitary conditions surrounding childbirth. Although few strictly scientific studies have been conducted among malnourished or deficient pregnant women, the few findings available do not show any inadequacy of immune response, nor complications following immunization. Such women should therefore be given the same vaccines usually administered to other expectant mothers.

THE IMMUNIZATION SCHEDULE

Table 3 :

THE IMMUNIZATION SCHEDULE
(EXPANDED PROGRAMME ON IMMUNIZATION, WHO)

IMMUNIZATION SCHEDULE	
Birth	BCG + Oral polio
6 weeks	DTP + Oral polio
10 weeks	DTP + Oral polio
14 weeks	DTP + Oral polio
9 months	Measles + (Yellow fever)

Remarks : If the schedule has not been respected, there is no need to begin the entire course over again. It should simply be resumed where it was left off. Malnutrition is not a contraindication for immunization. On the contrary, immunization is indispensable in such children, who are less resistant to infection than others.

Immunization with the BCG

The immunity involved here is cell-mediated, and is not transmitted from mother to child : it is most probably diminished in case of protein-energy malnutrition. The BCG may be administered from birth on, even in prematures. The response is measured by the intensity of post-vaccinal reaction to tuberculin.

Immunization against tetanus

It is performed at different dates, depending on whether the aim is to prevent neonatal tetanus or tetanus in an older child.

To prevent neonatal tetanus, it is preferable to take advantage of the transplacental transmission of antibodies from mother to child. The mother is therefore vaccinated before or during her pregnancy. These antibodies protect the child for several weeks, but since they have a relatively short duration, on the one hand, and the antigenicity of the vaccine is high, on the other hand, vaccination may elicit a satisfactory immune response in infants starting at age six weeks.

To prevent infantile tetanus, then, vaccination is performed from age six weeks on, in the form of three injections at intervals of at least one month. Boosters are required every ten years to maintain immunity throughout the person's lifetime.

Table 4 :

SCHEDULE FOR ANTI-TETANUS IMMUNIZATION OF WOMEN, AND CORRESPONDING DURATION OF PROTECTION

Number of doses	Minimum interval	Protection (percentage)	Duration of protection
1		0	0
2	4 weeks	80	3 years
3	3 months	95	5 years
4	1 year	99	10 years
5	1 year	99	Definitive

In a young woman who benefitted from the normal immunization schedule during the first year of their own life, the administration of a booster dose similar to the 3rd dose of the chart shown above is recommended, for the protection of her unborn children.

She should then be given the 4th and 5th doses at one-year intervals, to achieve definitive protection for her future children.

ATTENTION

Immunization against tetanus of women who are pregnant or of child-bearing age is the least often performed of all ; a scant third of all women around the world are protected.

Immunization against pertussis

Children may develop pertussis at any time after birth, since mothers do not transmit pertussis antibodies to their child. Vaccination is performed at six weeks, and only affords protection after the administration of three doses at intervals of at least one month. Since pertussis tends mostly to be serious for children under one, it is advisable immunize children as soon as possible, at 6, 10 and 14 weeks, so as to provide protection at the earliest possible date.

Immunization against poliomyelitis

Poliomyelitis is most often a latent digestive infection, which is only complicated by paralysis in one case out of one or two thousand. Children whose mother has been vaccinated or infected — as is the case for most mothers in developing countries — possess antibodies at birth, but these vanish within several weeks. The oral poliomyelitis vaccine, which elicits both humoral immune mechanisms and local mechanisms at the intestinal level, is effective from birth on since the local response is not inhibited by the maternal antibodies. The inactivated, injectable poliomyelitis vaccine is highly antigenic and is effective from the sixth week on. Both vaccines require at least three doses and boosters every ten years, if they are to afford complete protection.

Immunization against measles

As seen above, the maternal antibodies cross the placental barrier and protect the child during the first months of life. However, these same antibodies inhibit the child's immune response when vaccination is administered at too early a date. It is a fact that the measles virus is constantly present in communities of children, especially in overcrowded peri-urban areas, and infants may catch measles as soon as these short-lived protective antibodies disappear.

The immunization policy with respect to vaccination against measles therefore consists of a compromise between two risks : vaccinating too soon, which involves a risk of a high failure rate, or vaccinating later, where "later" may mean "too late" for some children who will already have contracted measles, with all of the attendant risks.

Immunization against hepatitis B

This vaccination is performed at birth, and is particularly important for neonates whose mothers are affected with this disease.

CONCLUSION

While certain immune deficiencies, either congenital (children infected by the HIV) or acquired (immunosuppressive treatment), may constitute contraindications for some vaccinations, there is no justification for refraining from immunization on the grounds of nutritional deficiency. At worst, vaccines may be slightly less effective than when the child's nutritional status is satisfactory, and when the immune reaction elicited by the vaccine is of the cell-mediated type. It is especially important to place emphasis on the immunization of persons with malnutrition or deficiencies, since many of these deficiencies result in increased fragility or sensitivity to infections (measles, pertussis,...). Indeed, such individuals often belong to those socioeconomic groups that are at greatest risk for certain types of pathology, some of which (including tuberculosis and neonatal tetanus) are avoidable through immunization.

BIBLIOGRAPHY

BEISEL W.R. Single nutrients and immunity. Amer. J. Clin. Nutr. 1982, 35, suppl. pp. 417-468.

CHANDRA R.K. Nutrition and immunology. Alan Liss, New York, 1988, 342 p.

CHANDRA R.K. Nutrition, immunity and infection : present knowledge and future directions. Lancet, 1983, pp. 668-691.

CHANDRA R.K. NEWBERNE P.M. Nutrition, immunity and infections ; Mechanisms of Interactions. Plenum Press, New York, 1977.

CORMAN L.C. Effects of specific nutrients on the immune response. Medical clinics of North America, 1985, 69, 4, pp. 759-791.

DARDENNE M. Le rôle du zinc dans le fonctionnement du système immunitaire. Cah. Nut. Diet. 1988, 23, 4, pp. 277-279.

DHUR A., GALAN P., HERCBERG S. Iron status, immune capacity and resistance to infections. Comp. Biochem. Physiol. 1989, 94, 1, pp. 11-19.

DILLON J.C. Nutrition, défenses immunitaires et infections. In : HERCBERG S. et al. Nutrition et Santé publique. Paris, Lavoisier, 1985, pp. 411-433.

DOND P. et al. The influence of undernutrition on immunity. Clin. Sci. 1984, 66, 3, pp. 241-248.

GREENWOOD B.M., WHITTLE H.C. Immunology of medecine in the tropics. E.L.B.S. Edward Arnol, Londres, 1981.

HERCBERG S. et al. Prevalence of iron deficiency and iron deficiency anaemia in Benin. Public Health, 1988, 102, pp. 73-83.

LAFAIX C. La rougeole, un modèle d'immunodépression acquis. In : M/S Médecine Sciences, Paris, n° spécial août 1990, pp. 12-18.

LAGRANGE P.H. et CRISCELLI C. Hôtes, microorganismes et réponses immunitaires. In : M/S Médecine Sciences, Paris, n° spécial août 1990, pp. 10-11.

KATZ S. Effects of malnutrition and parasitic infections on the immune response to vaccines. In : Recent advances in immunization. Scientific Publications, WHO, Washington DC, 1983, 451.

SCRIMSHAW N.S., TAYLOR C.E., GORDON J.E. Interactions of nutrition and infection. Monograph series, WHO, Geneva, 1968, 57.

FURTHER READING...

ROITT I., BROSTOFF J., MALE D. Immunology. Grover Medical publishing, 1989.

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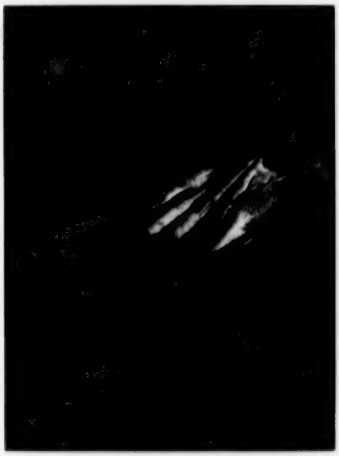

IMMUNITY AND NUTRITION

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The science of immunology has progressed extremely rapidly in recent years. One of the authors of the present volume presents a brief, simplified but complete review of present scientific understanding of immune defences.

Most public health-oriented research on individual nutritional status points to the existence of interactions between infection and nutrition disorders. On the basis of a broad overview of this question, the second author discusses its practical aspects : when, and against which diseases, should women, mothers and children in physiologically difficult situations — the malnourished, deficient, premature and immunocompised, in particular — be immunized ?

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